

EDITORIAL

C reactive protein and microvascular function

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Emerging data suggest that C reactive protein may be a mediator as well as a marker of atherosclerosis

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vasomotor dysfunction in the very early phases of atherogenesis.

A large body of evidence has shown that atherosclerosis is an inflammatory disease. Vascular inflammation contributes to the pathogenesis of atherosclerosis and, later in the disease process, is a major contributor to acute coronary syndromes.¹ Recently, it has been suggested that inflammation might play a key role also in microvascular dysfunction of patients with syndrome X (typical exertional chest pain, a positive exercise stress test response, and normal coronary angiogram).^{2–4} Triggers and pathways of inflammation are probably multiple and different in these different settings—that is, atherogenesis, acute coronary syndromes, and syndrome X. The identification of specific triggers and mechanisms of inflammation in each specific clinical setting might lead to new ways in its management.

INFLAMMATION AND ATHEROGENESIS

The triggers of inflammation in atherogenesis coincide with atherogenic stimuli like hypertension, hypercholesterolaemia, diabetes, and smoking. Through a variety of mechanisms, they enhance the production of reactive oxygen species, such as superoxide, that ultimately lead to activation of the vascular renin–angiotensin system as well as endothelial release of transcriptional and growth factors, proinflammatory cytokines, chemoattractant substances, and adhesion molecules.^{5–6} This complex cascade of events underlies the transition from normal endothelial function to endothelial dysfunction, resulting initially in abnormal vasomotor activity and then in atheroma formation. Several studies have documented a close relationship between the degree of inflammation and microvascular endothelial dysfunction. Fichtlscherer and colleagues⁷ found that patients with coronary artery disease and higher C reactive protein (CRP) concentrations, compared to those with lower CRP values, exhibited a reduced forearm vasodilator response to acetylcholine. Interestingly, normalisation of elevated CRP values over time was associated with a normalisation of endothelium mediated blood flow responses. Accordingly, Cleland and colleagues⁸ found that CRP concentrations correlate with basal forearm blood flow also in healthy subjects, thus further supporting the notion that inflammatory mechanisms play an important role in determining microvascular endothelium mediated

INFLAMMATION AND ACUTE CORONARY SYNDROMES

A growing body of data indicates that plaque inflammation plays a key role in the pathogenesis of unstable acute coronary syndromes, as cytokines secreted by activated inflammatory cells have the potential to activate the endothelium, transforming its antiaggregant and anticoagulant properties into aggregant and procoagulant properties.^{1–9} Furthermore, they may reduce matrix synthesis and increase its degradation, thus favouring plaque rupture.^{1–9} Plaque inflammation may also be responsible for the increased vasoreactivity of the culprit lesion observed in patients with unstable angina,¹⁰ as suggested by an increased tissue endothelin-1-like immunoreactivity at the site of the unstable atherosclerotic plaque.¹¹ In this regard, we have recently investigated the relation between systemic inflammation and coronary vasoreactivity at the site of the culprit lesion in patients with unstable angina. We found that elevated CRP concentrations are independently associated with enhanced vasoreactivity of the culprit lesion.¹² Indeed, patients with elevated CRP values exhibited both a greater dilation of the culprit lesion after intracoronary glyceryl trinitrate (an endothelium independent stimulus) and a greater constriction of the culprit lesion during cold pressor test (an endothelium dependent stimulus), thus suggesting in these patients both an enhanced resting tone of the culprit lesion and an alteration of endothelium dependent vasodilation. Of note, the uninvolved epicardial coronary segments exhibited similar responses in patients with normal and elevated CRP concentrations, supporting the concept that the enhanced vasoreactivity is a local plaque related phenomenon.¹² Therefore, inflammation is likely to play a pivotal role in both the key pathogenetic components of acute coronary syndromes—plaque disruption with superimposed thrombosis and enhanced vasoreactivity of the culprit lesion.

The role of inflammation in coronary microcirculatory dysfunction in the setting of acute coronary syndromes is still poorly known. It is well established that coronary microvascular function plays an important modulatory role in the pathophysiology of myocardial ischaemia in patients with unstable angina.¹³ Our preliminary findings obtained in non-culprit arteries of patients with unstable angina showed that elevated CRP concentrations are associated with a lesser increase of coronary blood flow during both endothelium dependent and endothelium

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independent stimuli, thus suggesting that inflammatory mechanisms may cause a generalised coronary microvascular dysfunction in these patients (unpublished data).

INFLAMMATION AND SYNDROME X

It has recently been suggested that inflammation is also involved in coronary microcirculation abnormalities observed in patients with cardiac syndrome X.²⁻⁴ Both endothelial cell activation and coronary endothelial dysfunction have been reported in these patients, which may result in an increased release of constricting factors and the production of pro-inflammatory cytokines, cell adhesion molecules, and growth factors responsible, in turn, for microvascular dysfunction. Recently, Tousoulis and colleagues³ reported higher intercellular cell adhesion molecule 1 and vascular cell adhesion molecule 1 values in patients with cardiac syndrome X, compared with healthy individuals. Moreover, Cosin-Sales and colleagues⁴ reported that CRP values correlate with symptoms and ECG markers of myocardial ischaemia in these patients, thus suggesting that inflammatory mechanisms may be responsible, at least in part, for endothelial dysfunction and increased disease activity in patients with cardiac syndrome X.

The article by Teragawa and colleagues¹⁴ in this issue of *Heart* provides new insights into the relation between inflammation and coronary microcirculatory dysfunction. They investigated the relation between CRP concentrations and coronary microvascular endothelial function in 46 Japanese patients with atypical chest pain and angiographically normal coronary arteries. They found that CRP values are inversely and independently correlated with acetylcholine induced changes in coronary blood flow. In keeping with previous studies showing a close relation between inflammation and peripheral endothelial function^{7,8} in patients with cardiac syndrome X,²⁻⁴ this study further suggests a close relation between inflammatory mechanisms and coronary microvascular dysfunction. A limitation of this study is the poor clinical characterisation of the patients. Indeed, it is not clear whether the association between endothelial dysfunction in coronary microcirculation and raised CRP occurs in the setting of early atherosclerosis or cardiac syndrome X.

IMPLICATIONS

Besides their role in atherogenesis and in acute coronary syndromes, inflammatory mechanisms are likely to also play a role in coronary microvascular dysfunction. However, triggers and mechanisms of inflammation in this setting are largely unknown and probably different to those involved in the two other pathophysiological conditions. Therefore, specific mechanisms of microvascular dysfunction caused by inflammation should be further investigated in order to establish tailored therapeutic strategies. Of note, emerging data suggest that CRP may be a mediator as well as a marker of atherosclerosis. In fact, CRP induces expression of cellular adhesion molecules, interleukin-6, and endothelin-1 by endothelial cells.¹⁵ CRP also mediates monocyte chemoattractant protein-1 induction,¹⁶ and it has been shown to mediate uptake of low density lipoprotein by macrophages.¹⁷ Furthermore, CRP attenuates nitric oxide production and

inhibits angiogenesis¹⁸ and, very recently, has been shown to upregulate angiotensin type 1 receptors in vascular smooth muscle¹⁹ and to decrease prostacyclin release from endothelial cells.²⁰ Thus, lowering CRP concentrations by, for example, use of statins and/or aspirin,²¹ might improve coronary microvascular dysfunction. Whether this is a valid approach, however, is still unknown and deserves further investigation. Indeed, as mediators of inflammation are multiple, the strategy of indentifying triggers and mechanisms of inflammation in each specific clinical setting and directing treatment at the specific triggers or to rate limiting steps in effector pathways appears more reasonable.

REFERENCES

- Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135-43.
- Desideri G, Gaspardone A, Gentile M, et al. Endothelial activation in patients with cardiac syndrome X. *Circulation* 2000;**102**:2359-64.
- Tousoulis D, Davies GJ, Asimakopoulou G, et al. Vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 serum level in patients with chest pain and normal coronary arteries (syndrome X). *Clin Cardiol* 2001;**24**:301-4.
- Cosin-Sales J, Pizzi C, Brown S, et al. C-reactive protein, clinical presentation, and ischemic activity in patients with chest pain and normal coronary angiograms. *J Am Coll Cardiol* 2003;**41**:1468-74.
- Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. *Am J Med* 1998;**105**:32-9S.
- Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000;**87**:840-4.
- Fichtlscherer S, Rosenberger G, Walter DH, et al. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 2000;**102**:1000-6.
- Cleland SJ, Sattar N, Petrie JR, et al. Endothelial dysfunction as a possible link between C-reactive protein levels and cardiovascular disease. *Clin Sci* 2000;**98**:531-5.
- Crea F, Biasucci LM, Buffon A, et al. Role of inflammation in the pathogenesis of unstable coronary artery disease. *Am J Cardiol* 1997;**80**(5A):10E-16E.
- Bogaty P, Hackett D, Davies G, et al. Vasoreactivity of the culprit lesion in unstable angina. *Circulation* 1994;**90**:5-11.
- Zeiber AM, Goebel H, Schachinger V, et al. Tissue endothelin-1 immunoreactivity in the active coronary atherosclerotic plaque. A clue to the mechanism of increased vasoreactivity of the culprit lesion in unstable angina. *Circulation* 1995;**91**:941-7.
- Tomai F, Crea F, Gaspardone A, et al. Unstable angina and elevated C-reactive protein levels predict enhanced vasoreactivity of the culprit lesion. *Circulation* 2001;**104**:1471-6.
- Marzilli M, Sambucetti G, Fedele S, et al. Coronary microcirculatory vasoconstriction during ischemia in patients with unstable angina. *J Am Coll Cardiol* 2000;**35**:327-34.
- Teragawa H, Fukuda Y, Matsuda K, et al. Relation between C reactive protein concentrations and coronary microvascular endothelial function. *Heart* 2004;**90**:750-4.
- Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000;**102**:2165-8.
- Pasceri V, Chang J, Willerson JT, Yeh ET. Modulation of C-reactive protein mediated-monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. *Circulation* 2001;**103**:2531-4.
- Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. *Circulation* 2001;**103**:1194-7.
- Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002;**106**:913-9.
- Wang CH, Li SH, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation* 2003;**107**:1783-90.
- Venugopal SK, Devaraj S, Jialal I. C-reactive protein decreases prostacyclin release from human aortic endothelial cells. *Circulation* 2003;**108**:1676-8.
- Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein: the cholesterol and recurrent events (CARE) investigators. *Circulation* 1999;**100**:230-5.